Remarks

Claims 22-29, 34-41, 46 and 47 are pending in this application. Claims 26-29 and claims 38-41 have been cancelled without prejudice or disclaimer. Claims 1 and 36 have been amended without prejudice or disclaimer. No new matter has been added with these amendments. Applicants reserve the right to prosecute any cancelled or otherwise unclaimed subject matter in this or a separate application, as appropriate. Consideration and entry of these remarks and amendments is respectfully requested.

A. Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 22-29, 34-41, 46 and 47 stand rejected under 35 U.S.C. 112, first paragraph as failing to comply with the enablement requirement. The Examiner alleges that the specification "does not provide guidance for MHC class II molecules as claimed" (Final Office Action dated 11/02/07, p. 3). In this amendment, the limitation relating to a "class II beta-2-microglobulin HLA monomer and a folding peptide" has been removed. As the pending rejection was made against the previously pending claims, the rejection is moot. However, the Examiner also alleged that "the synthesis of class II MHC monomers at the time of the invention was not well known in the art" (Final Office Action dated 11/02/07, pp. 3-4). As the amended claims require the use of recombinant class II MHC or MHC-type molecules, Applicants provide the following comments regarding this particular issue.

The Examiner alleged: "[a]t best, one of skill in the art would have to perform random experimentation to try and construct a recombinant MHC Class II monomer that would function as claimed and random experimentation is undue." The Examiner supported these allegations by referring to Barnardo (Transplantation, Vol. 70, No. 3, pp. 531-536, Aug. 15, 2000), U.S. Pat. No. 6,727,070 ("Thomas"), Frayser et al. (Protein Expression and Purification, 15, pp. 105-114, 1999) and Armilli et al. (J. Biol. Chem., Vol. 270, No. 2, pp. 971-977 (1995)). These references are characterized as teaching that there were difficulties associated with expressing recombinant MHC or MHC-type Class II molecules. Applicants respectfully disagree with these characterizations and the Examiner's allegations.

First, Applicants believe the Examiner has mischaracterized the supporting references. Although the Barnardo reference states that "...the synthesis of class II monomer has not been reported", both Frayser and Arimilli demonstrate the synthesis of recombinant MHC or MHC-type molecules. At p. 105, col. 2, Frayser characterizes selected prior work as reproduced below:

> Previous efforts to prepare recombinant complexes of class II MHC proteins with single, defined peptides (8-12) or empty, peptide-free molecules (9, 10, 13, 14) have met with limited success.

However, Frayser characterizes the work presented in their paper as follows:

> We have folded DR1 in the absence of peptide and isolated a soluble, peptide-free αβ-heterodimer. The empty DR1 can bind antigenic peptide. (p. 105 (Abstract))
>
> The empty HLA-DR1 is significantly more stable than empty class I MHC proteins...or class I complexes with weakly binding peptides. . . . (p. 113)

Similarly, Arimilli characterizes prior work as having encountered obstacles, but characterizes their own work as shown below:

> In this report, we describe the refolding of E. coli-expressed recombinant human α and β chains lacking the transmembrane regions followed by reconstitution of biologically active HLA DR2. (p. 971-2)
>
> In conclusion, results presented here demonstrate the formation of functionally active HLA DR2 heterodimeric complexes containing antigenic epitopes. The yield of such complexes is approximately 800-fold higher than the native DR2 molecules. (p. 976)

Thus, both Frayser and Arimilli successfully prepared functoinal recombinant MHC or MHC-type Class II molecules. While Thomas' views may apply generally to other proteins, the same are clearly not applicable to recombinant MHC or MHC-type Class II molecules. In contrast to the Examiner's position, then, expression of recombinant MHC or MHC-type Class II molecules was known as of the filing date of the instant specification.

Second, Applicants disagree with the Examiner's allegation that to carry out the claimed invention "one of skill in the art would have to perform random experimentation...and random experimentation is undue." It is well-established that a specification may enable a claim where some experimentation is required so long as it is not undue. *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200 (Fed. Cir. 1991); *DeGeorge v. Bernier*, 768 F.2d 1318 (Fed. Cir. 1985). Some trial and error experimentation is permissible. *W.L. Gore & Assoc. v. Garlock, Inc.* 721 F.2d 1540 (Fed. Cir. 1983). In contrast to the Examiner's allegation, "random experimentation" (e.g., trial and error experimentation) is not necessarily undue. Accordingly, a rejection based on this reasoning would be improper.

Applicants respectfully maintain that the Examiner's reasoning cannot support a 35 U.S.C. 112, first paragraph enablement rejection of the amended claims. The specification provides sufficient guidance to one of skill in the art. The skilled artisan would be required to practice nothing more than routine experimentation in carrying out the claimed method. *AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1244 (Fed. Cir. 2003).

B. Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 22-29, 34-41, 46 and 47 stand rejected under 35 U.S.C. 112, second paragraph as being indefinite. Applicants respectfully traverse these rejections as indicated below.

1. "Recombinant MHC-type molecules"

Claim 22, upon which claims 22-29, 34 and 35 depend, stands rejected as to the term "recombinant MHC-type molecules" (amended herein to "recombinant MHC-type Class II molecules"). The Examiner alleges that the meaning of this term is unclear. Applicants maintain that the skilled artisan would understand the meaning of the term "recombinant MHC-type Class II molecules" from the specification (US 2004/0191245A1, paragraphs [0016]–[0040]). As described therein, MHC-type molecules include derivatives, variants or fragments of MHC molecules that maintain the desired function (e.g., "functioning as anti-MHC antibody antigens", "sufficiently antigenic to be bound by anti-MHC antibodies", "present the extracellular polymorphic

residue...for binding by the anti-MHC antibody", "allow appropriate presentation of one or more epitopic sites of the MHC allele of interest"). The types of modifications that may be made to MHC molecules to produce "recombinant MHC-type Class II molecules" are also described (e.g., "maintenance of not only residues at the epitopic site, but also key skeletal residues to achieve correct folding", "by single or multiple amino acid...substitution, addition and/or deletion but which nonetheless retains functional activity", "amino and/or carboxy terminal fusion proteins", "conservative amino acid substitutions"). The meaning of the term "recombinant MHC-type Class II molecules" as instantly claimed and described by Applicants' specification is clear. Applicants believe the skilled artisan would understand which molecules are "recombinant MHC-type Class II molecules" in the context of the instant claims and which are not. Applicants believe the term is clear from the instant claims and specification and respectfully request withdrawal of this rejection.

2. "Folding peptide"

Claim 22 stands rejected as to the term "folding peptide". Claim 22 has been amended to delete reference to "folding peptide". The rejection is therefore moot.

3. "Recombinant HLA-type molecules"

Claim 36 stands rejected as to the term "recombinant HLA-type molecules" (amended herein to "recombinant HLA-type Class II molecules"). The Examiner alleges that the meaning of this term is unclear. Applicants maintain that the skilled artisan would understand the meaning of the term "recombinant HLA-type Class II molecules" from the specification (US 2004/0191245A1, paragraphs [0016]–[0040]). For instance, the instant specification functionally defines an "HLA-type" molecule at paragraph [0037] as one "exhibiting the properties and characteristics of an HLA molecule." Both the HLA molecules and the functions thereof are known to one of skill in the art. The specification also describes the types of "recombinant MHC-type Class II molecules" (a genus to which HLA-type molecules belong) as including derivatives, variants or fragments of MHC molecules that maintain the desired function (e.g., "functioning as anti-MHC antibody antigens", "sufficiently antigenic to be bound by anti-MHC

antibodies", "present the extracellular polymorphic residue...for binding by the anti-MHC antibody", "allow appropriate presentation of one or more epitopic sites of the MHC allele of interest"). The types of modifications that may be made are also described as including, for example, "maintenance of not only residues at the epitopic site, but also key skeletal residues to achieve correct folding"; "single or multiple amino acid...substitution, addition and/or deletion but which nonetheless retains functional activity"; "amino and/or carboxy terminal fusion proteins" and, "conservative amino acid substitutions", among others. The meaning of the term "recombinant HLA-type Class II molecules" as instantly claimed and described by Applicants' specification is clear. Applicants believe the skilled artisan would understand which molecules are "recombinant HLA-type Class II molecules" in the context of the instant claims and which are not. Applicants believe the term is clear from the instant claims and specification and respectfully request withdrawal of this rejection.

Conclusions

Applicants believe that a full and complete Reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned. Prompt and favorable consideration of this Reply is respectfully requested.

Respectfully Submitted,

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